



King's Research Portal

DOI:

[10.1016/j.exger.2018.04.017](https://doi.org/10.1016/j.exger.2018.04.017)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Vancampfort, D., Stubbs, B., Lara, E., Vandebulcke, M., Swinnen, N., Smith, L., Firth, J., Herring, M. P., Hallgren, M., & Koyanagi, A. (2018). Mild cognitive impairment and sedentary behavior: A multinational study. *Experimental Gerontology*, 108, 174-180. <https://doi.org/10.1016/j.exger.2018.04.017>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

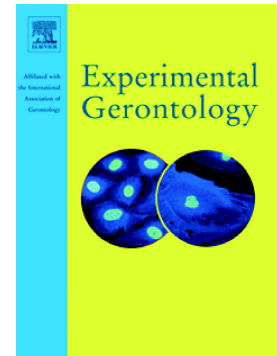
Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

Mild cognitive impairment and sedentary behavior: A multinational study

Davy Vancampfort, Brendon Stubbs, Elvira Lara, Mathieu Vandenbulcke, Nathalie Swinnen, Lee Smith, Joseph Firth, Matthew P. Herring, Mats Hallgren, Ai Koyanagi



PII: S0531-5565(17)30882-3
DOI: doi:[10.1016/j.exger.2018.04.017](https://doi.org/10.1016/j.exger.2018.04.017)
Reference: EXG 10343
To appear in: *Experimental Gerontology*
Received date: 11 December 2017
Revised date: 4 April 2018
Accepted date: 19 April 2018

Please cite this article as: Davy Vancampfort, Brendon Stubbs, Elvira Lara, Mathieu Vandenbulcke, Nathalie Swinnen, Lee Smith, Joseph Firth, Matthew P. Herring, Mats Hallgren, Ai Koyanagi , Mild cognitive impairment and sedentary behavior: A multinational study. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Exg(2017), doi:[10.1016/j.exger.2018.04.017](https://doi.org/10.1016/j.exger.2018.04.017)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Mild cognitive impairment and sedentary behavior: a multinational study

Davy Vancampfort^{*1,2}, Brendon Stubbs^{3,4,5}, Elvira Lara^{6,7}, Mathieu Vandenbulcke⁸, Nathalie Swinnen²,
 Lee Smith⁹, Joseph Firth^{10,11}, Matthew P. Herring^{12,13}, Mats Hallgren¹⁴, Ai Koyanagi^{7,15}

1. KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium
2. KU Leuven, University Psychiatric Center KU Leuven, Kortenberg, Belgium
3. Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill,
 London, UK
4. Health Service and Population Research Department, Institute of Psychiatry, Psychology and
 Neuroscience, King's College London, De Crespigny Park, London, UK
5. Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, UK
6. Department of Psychiatry, Universidad Autónoma de Madrid, Madrid, Spain
7. Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental,
 CIBERSAM, Madrid, Spain
8. Old Age Psychiatry, University Psychiatric Centre KU Leuven, Belgium.
9. The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge,
 UK.
10. NICM, School of Science and Health, University of Western Sydney, Australia
11. Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of
 Manchester, UK
12. Department of Physical Education and Sport Sciences, University of Limerick, Limerick, Ireland
13. Health Research Institute, University of Limerick, Limerick, Ireland
14. Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
15. Research and Development Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona,
 Fundació Sant Joan de Déu, Dr. Antoni Pujadas, Barcelona, Spain

***Corresponding author:** Davy Vancampfort, Tervuursevest 101, 3001 Leuven, Belgium. Tel.: +32 2
 758 05 11; Fax: +32 2 759 9879.

Abstract

Background: Sedentary behavior (SB) is associated with poor cognitive performance. However, the contribution of sedentary time to risk of mild cognitive impairment (MCI) remains unclear. This study assessed the association of SB with MCI in six low- and middle-income countries.

Methods: The Study on Global Ageing and Adult Health (SAGE) survey included 34,129 adults aged ≥ 50 years [mean (SD) age 62.1 (15.6) years; 51.7% females]. SB was self-reported and expressed as a categorical variable [< 8 or ≥ 8 hours per day (high SB)]. The definition of MCI was based on the recommendations of the National Institute on Ageing-Alzheimer's Association. Multivariable logistic regression analysis was conducted to assess the association between SB and MCI.

Results: The overall prevalence (95%CI) of MCI and high SB (i.e., ≥ 8 h/day) were 15.3% (14.4%-16.3%) and 10.1% (9.0%-11.3%), respectively. After adjustment for potential confounders, being sedentary for ≥ 8 h/day was associated with a 1.56 (95%CI=1.27-1.91) times higher odds for MCI. A one-hour increase in SB was associated with a 1.08 (95%CI=1.05-1.11) times higher odds for MCI.

Conclusion: Our study results highlight the need to further explore a sedentary lifestyle as a potential risk factor for MCI or subsequent dementia. Longitudinal and intervention studies are warranted to confirm/refute the current findings.

Keywords: mild cognitive impairment; dementia; sedentary; sitting

1. Introduction

Dementia is one of the main causes of disability and dependency in the expanding older adult population worldwide (Wimo and others 2017). Currently, it is estimated that approximately 50 million people worldwide are diagnosed with dementia, and this figure is projected to increase to 132 million by 2050 (Prince 2015). The prevalence and incidence of dementia is increasing rapidly in low- and middle-income countries (LMICs), placing immense pressure on the social and economic systems in this part of the world (Wimo and others 2017). Specifically, the proportion of those with dementia residing in LMICs are expected to increase from 58% in 2015 to 68% in 2050 (Alzheimer's Disease International 2015).

The greatly increasing numbers of people with dementia in LMICs are attributed to the increase in life expectancy and the concurrent rise in other modifiable risk factors, such as unhealthy lifestyle behaviors (Ferri and Jacob 2017; Prince and others 2009). Since there is currently no treatment available to alter the clinical course of dementia significantly (Cummings 2004; Kadoszkiewicz and others 2005), identifying modifiable risk factors in the precursory stages of dementia is considered a priority to prevent or delay the onset of dementia (Livingston and others 2017). Specifically, mild cognitive impairment (MCI) is considered to be a preclinical state of dementia (Albert and others 2011) for which targeted interventions may be possible. Previously reported potentially modifiable risk factors for MCI include factors such as low physical activity levels, obesity, diabetes, and hypertension (Lara and others 2016).

In the past decade, sedentary behavior has emerged as an important risk factor for various health outcomes in adult populations (Keadle and others 2017). Sedentary behavior refers to any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture (Tremblay and others 2017). It is associated with a range of deleterious outcomes such as diabetes, cancer, cardiovascular diseases, and premature mortality, largely independent of physical activity (Biswas and others 2015; Powell and others 2017). More recently, there has been growing interest in its relation with mental health. For example, recent meta-analyses have found a positive relationship between more time spent sedentary and depression (Zhai and others 2015) and this was also independent from physical activity levels. While a systematic review (Falck and others 2017a) showed that sedentary behavior is also associated with lower

cognitive performance, none were specifically executed in MCI and therefore the attributable risk of sedentary time to MCI still remains unclear.

To the best of our knowledge, the only study on this topic to date found that Canadian community-dwelling people with MCI (n=82) (at least 55 years old) spent a greater number of ≥ 30 min bouts/day sedentary per day than those without MCI (n=69) (4.1 ± 1.8 versus 3.3 ± 1.7 , $P=0.046$) (Falck and others 2017b). However, this study was conducted in a limited geographical area in a single high-income country and was of small sample size, limiting generalizability to other settings. Furthermore, it remains to be explored whether more time spent sedentary is associated with a higher risk for MCI. Given that there are no multinational, community-based, or nationally representative studies on the association between sedentary behavior and MCI, and that there are no studies on this topic from LMICs, we aimed to assess the association between time spent sedentary and MCI among adults aged ≥ 50 years in six LMICs using data from the WHO Global Ageing and Adult Health study (SAGE). We included the middle-aged ($50 \leq 65$ years) in this analysis as intervening in mid-life has been reported to be important to prevent the later onset of dementia (Alzheimer's Disease International 2014; Gottesman and others 2017; Johansson and others 2010; Kivipelto and others 2006). Exploring the association between time spent sedentary and MCI in LMICs is of particular importance given the increasing rates of sedentary lifestyles (Christensen and others 2009; Vancampfort and others 2017b) and dementia and cognitive impairment in this part of the world (Prince and others 2016). Next to this, there is a lack of knowledge regarding the risks associated with sedentary behavior in LMICs (Pengpid and others 2015). Furthermore, the continuing dearth of studies from LMICs also highlights the gap between where research is conducted and where the largest public health impacts of sedentary behavior occur (Sallis and others 2016).

2. Methods

2.1. The survey

Data from the SAGE were analyzed. These data are publically available through <http://www.who.int/healthinfo/sage/en/>. This survey was undertaken in China, Ghana, India, Mexico, Russia, and South Africa between 2007 and 2010. These countries broadly represent different geographical locations and levels of socio-economic and demographic transition. Based on the World Bank classification at the time of the survey, Ghana was the only low-income country, and China and India were lower middle-income countries although China became an upper middle-income country in 2010. The remaining countries were upper middle-income countries.

Details of the survey methodology have been published elsewhere (Kowal and others 2012). In brief, in order to obtain nationally representative samples, a multistage clustered sampling design method was used. The sample consisted of adults aged ≥ 18 years with oversampling of those aged ≥ 50 years. Trained interviewers conducted face-to-face interviews using a standard questionnaire. Standard translation procedures were undertaken to ensure comparability between countries. If a respondent was unable to undertake the interview because of limited cognitive function, a separate questionnaire was administered to a proxy respondent. These individuals were however not included in the current study. The survey response rates were: China 93%; Ghana 81%; India 68%; Mexico 53%; Russia 83%; and South Africa 75%. Sampling weights were constructed to adjust for the population structure as reported by the United Nations Statistical Division. Ethical approval was obtained from the WHO Ethical Review Committee and local ethics research review boards. Written informed consent was obtained from all participants.

2.2. Mild cognitive impairment (MCI) (Outcome)

MCI was ascertained based on the recommendations of the National Institute on Aging-Alzheimer's Association (Albert and others 2011). We applied the identical algorithms used in previous publications using datasets including the SAGE with the same survey questions to identify MCI (Lara and others 2017; Lara and others 2016; Vancampfort and others 2017c). Briefly, individuals fulfilling all of the following conditions were considered to have MCI:

(a) Concern about a change in cognition: Individuals who replied 'bad' or 'very bad' to the question "How would you best describe your memory at present?" and/or those who answered 'worse' to the

question “Compared to 12 months ago, would you say your memory is now better, the same or worse than it was then?”.

(b) Objective evidence of impairment in one or more cognitive domains: was based on a <-1 SD cut-off after adjustment for level of education, age, and country. Cognitive function was assessed through the following performance tests: word list immediate and delayed verbal recall from the Consortium to Establish a Registry for Alzheimer's Disease (Morris and others 1989), which assessed learning and episodic memory; digit span forward and backwards from the Wechsler Adult Intelligence Scale (The Psychological Corporation 2002), that evaluated attention and working memory; and the animal naming task (Morris and others 1989), which assessed verbal fluency.

(c) Preservation of independence in functional abilities: was assessed by questions on self-reported difficulties with basic activities of daily living (ADL) in the past 30 days (Katz and others 1963). Specific questions were: “How much difficulty did you have in getting dressed?” and “How much difficulty did you have with eating (including cutting up your food)?” The answer options were none, mild, moderate, severe, and extreme (cannot do). Those who answered either none, mild, or moderate to both of these questions were considered to have preservation of independence in functional activities. All other individuals were deleted from the analysis (935 individuals aged ≥ 50 years).

(d) No dementia: Individuals with a major cognitive impairment that precludes the possibility to undertake the survey were not included in the current study.

2.3. Sedentary behavior (*Exposure variable*)

In order to assess sedentary behavior, participants were asked to state the total time they usually spent (expressed in minutes per day) sitting or reclining including at work, at home, getting to and from places, or with friends (e.g., sitting at a desk, sitting with friends, travelling in car, bus, train, reading, playing cards or watching television). This did not include time spent sleeping. Sedentary behavior was assessed as a continuous variable (hours per day) and also as a categorical [<8 or ≥ 8 hours per day (high sedentary behavior)] variable. The eight-hour cut-off was chosen as previous research indicated that being sedentary for ≥ 8 hours/day in the general population is associated with a higher risk for premature mortality (Ekelund and others 2016). This measure has been shown to

have excellent convergent validity in grading a plethora of psychosocial variables (Vancampfort and others 2017a; Vancampfort and others 2017b).

2.4. Control variables

The analysis adjusted for a number of potential confounders which have been reported to be linked with both MCI and sedentary behavior (Lara and others 2016; Vancampfort and others 2017a). These included sex, age (years), years of education, wealth quintiles based on country-specific income, depression, obesity, number of chronic physical conditions, and low physical activity. Questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview (Kessler and Ustun 2004) were used for the endorsement of DSM-IV depression. A stadiometer and a routinely calibrated electronic weighting scale were used to measure height and weight respectively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as $BMI \geq 30 \text{ kg/m}^2$. The total number of seven chronic physical conditions (angina, arthritis, asthma, chronic lung disease, diabetes, hypertension and stroke) was summed per individual. Diabetes and stroke were solely based on lifetime self-reported diagnosis. Blood pressure was measured three times with a one-minute interval with the use of a wrist blood pressure monitor. Hypertension was defined as having at least one of: systolic blood pressure $\geq 140 \text{ mmHg}$; diastolic blood pressure $\geq 90 \text{ mmHg}$; or self-reported diagnosis. For angina, arthritis, asthma, and chronic lung disease, the participant was considered to have the condition in the presence of self-reported diagnosis and/or symptom-based diagnosis using algorithms. Specifically, the validated Rose questionnaire was used for angina (Rose 1962), and other previously validated symptom-based algorithms were used for arthritis, asthma, and chronic lung disease (Arokiasamy and others 2017; Moussavi and others 2007). The Global Physical Activity Questionnaire (Bull and others 2009) was used to assess levels of physical activity. The total amount of moderate-to-vigorous physical activity in a typical week was calculated based on self-report. Those scoring ≥ 150 minutes of moderate-to-vigorous intensity physical activity were classified as meeting the recommended guidelines (coded = 0), and those scoring < 150 minutes (low physical activity) were classified as not meeting the recommended guidelines (coded = 1) (World Health Organization, 2010).

2.5. Statistical analysis

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). The analysis was restricted to those aged ≥ 50 years due to the age-related nature of MCI. We conducted multivariable logistic regression analysis to assess the association between sedentary behavior (exposure) and MCI (outcome) using the overall sample (i.e., age ≥ 50 years) and by age groups (50-64 and ≥ 65 years) as previous studies have shown that the risk factors of MCI may differ between mid-life and late-life (Baumgart and others 2015; Lara and others 2016). Total sedentary behavior was included in the model as a continuous variable (hours per day) and also as a categorical variable [< 8 or ≥ 8 hours per day (high sedentary behavior)]. We also conducted country-wise analyses using the sample including all individuals aged ≥ 50 years with high sedentary behavior as the exposure variable.

The regression analyses were all adjusted for sex, age, years of education, wealth, depression, obesity, number of chronic physical conditions, low physical activity, and country with the exception of the country-wise analysis which did not adjust for country. Country adjustment was done by including dummy variables for each country. Less than 4.7% of the data were missing for the variables used in the analysis, therefore imputation was considered unnecessary. All variables were included in the models as categorical variables with the exception of age, years of education, number of chronic physical conditions, and sedentary behavior when used as a continuous variable. Complete-case analysis was performed. The sample weighting and the complex study design were taken into account in the analyses. Results from the regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The level of statistical significance was set at $P < 0.05$.

3. Results

The final analytical sample comprised 32,715 individuals aged ≥ 50 years (China $n=12,815$; Ghana $n=4,201$; India $n=6,191$; Mexico $n=2,070$; Russia $n=3,766$; South Africa $n=3,672$). Sample characteristics are presented in **Table 1**. Overall, the mean (SD) age was 62.1 (15.6) years and 51.7% were females. The overall prevalence (95%CI) of MCI and high sedentary behavior (i.e. ≥ 8 h/day) were 15.3% (14.4%-16.3%) and 10.1% (9.0%-11.3%), respectively.

Insert Table 1 about here

The prevalence of MCI increased with increasing hours per day spent sedentary (**Figure 1**). Specifically, the prevalence of MCI increased from 13.5% in individuals who are sedentary for <4 hours/day to 21.3% among those sedentary for ≥ 11 hours/day.

Insert Figure 1 about here

After adjustment for potential confounders, being sedentary for ≥ 8 h/day was associated with a 1.56 (95%CI=1.27-1.91) times higher odds for MCI in the overall sample (**Table 2**). The corresponding figures for those aged 50-64 years and ≥ 65 years were 1.34 (1.02-1.76) and 1.70 (1.27-2.28), respectively.

Insert Table 2 about here

A one-hour increase in sedentary behavior was associated with a 1.08 (95%CI=1.05-1.11) times higher odds for MCI in the overall sample (**Table 3**), with similar estimates being obtained for the younger and older age groups.

Insert Table 3 about here

Country-wise analyses showed that highly sedentary behavior is associated with MCI (OR 1.34-2.83) in China, Mexico, South Africa, and India although the result of Mexico was not statistically significant (**Figure 2**).

Insert Figure 2 about here

4. Discussion

4.1. General findings

To the best of our knowledge, the current study is the first to demonstrate that more time spent sedentary is associated with a higher odds for MCI in six low- and middle-income countries which collectively, comprise nearly half of the worldwide population (Kowal and others 2012). More in detail, being sedentary for ≥ 8 h/day was associated with a 1.56 (95%CI=1.27-1.91) times higher odds for MCI in the overall sample. Sedentary behavior was similarly associated with MCI in both the middle-aged and the older population. The strengths of the study include the large sample size and the use of nationally representative samples from six countries. Given the increase in risk factors for dementia (e.g., low physical activity, chronic diseases such as diabetes, obesity) and rapid aging, our study results highlight the need for further exploration of sedentary lifestyle as a potential risk factor for MCI and dementia in this setting through longitudinal cohort designs.

4.2. Interpretation of findings

Previous research suggested that a sedentary lifestyle has been associated with poor cognitive performance (Falck and others 2017a and b; Ku and others 2017). However, none of these studies were specifically on MCI. The potential mechanisms on how sedentary behavior may negatively influence cognitive function are not clear at this stage and future longitudinal research is needed to confirm/refute our findings. Nonetheless, it has been hypothesized that the established negative consequences of sedentary behavior on glucose metabolism, diabetes risk, obesity and cardiovascular disease (Biswas and others 2015; Vancampfort and others 2017b), all of which are risk factors for MCI (Lara and others 2016), could potentially act to increase the risk of cognitive deterioration in older age. Also, the unfavorable inflammatory profile associated with sedentary behavior in older adults, including increased c-reactive protein, interleukin-6 and tumor necrosis factor alpha (Wirth and others 2017), could contribute to cognitive decline (Sartori 2013). Nevertheless, the current evidence regarding underlying biochemical or neurobiological markers in older adults is still

limited (Wirth et al., 2017) and future research is required. Next to these physiological mechanisms, there is a growing body of evidence suggesting that a sedentary lifestyle increases the risk of mental illness such as depression (Schuch and others 2017; Schuch and others 2016), which is itself a risk factor that has been associated with MCI (Lara and others 2017). However, in the current study we did adjust for depression as a potential factor underlying the sedentary behavior – MCI relationship. Finally, environmental and socio-cultural factors including alcohol use habits might also affect the sedentary lifestyle – MCI relationship. We did find a moderate level of between-country heterogeneity in the association between sedentary lifestyle and MCI, however the exact reasons remain unclear and should be investigated.

4.3. Policy implications and directions for future research

Given the findings of our study and the wider literature from longitudinal research considering the deleterious impact of sedentary behavior on multiple health outcomes (Biswas et al., 2015), it is essential that public health interventions should seek to limit the time spent sedentary and future studies should consider how such interventions impact cognitive function. Such campaigns and interventions could include messages on interrupting periods of prolonged sitting and specifically increasing light physical activity which has favorable cognitive benefits (Stubbs and others 2017). Our findings also resonate recent clinical recommendations by Falck and others (2017a). The authors advice clinicians to promote healthy cognitive aging among their patients by recommending them to increase their physical activity levels up to ≥ 150 minutes/week, while concomitantly limiting sedentary behavior. Finally, although application of self-monitoring devices and alarms are not easy to implement among higher risk groups in low resource settings, a recent International mobile-health intervention on physical activity, sitting, and weight using light-weight, low-cost, non-interactive pedometers as a self-monitoring and motivational tool demonstrated reductions in sedentary time. In a 100-day program, participants were encouraged to increase incidental activity such as using stairs and avoidance of sitting. After 100 days, the time spent sedentary reduced in low-income countries by 0.73h per day (95%CI= -0.75 to -0.70h) and by 0.59h per day 95%CI= -1.08 to -0.10h) in middle-income countries (Ganesan and others 2016). Such interventions may be valuable to reduce time spent sedentary in LMICs, and assessment of whether they may also mitigate the risk for MCI or subsequent dementia is warranted.

4.4. Limitations

The current study results should be interpreted in light of several limitations. First, some individuals with mild dementia may have been included in our analytical sample owing to the fact that the study was not designed to make clinical diagnoses of dementia. However, it is reassuring that the prevalence of MCI in our study was within previously reported figures (Petersen 2016). Second, there is currently no consensus in terms of the acceptable level of functional impairment that individuals with MCI could present (Lindbergh and others 2016). We used a conservative definition for preservation of independence in functional abilities, which has been used in previous publications (Lara and others 2017; Lara and others 2016), so as not to exclude MCI cases with disability not related with their cognitive ability. It is possible that the results may differ slightly depending on the definition used. Third, sedentary behavior was captured with a self-report measure, the accuracy of which has been questioned (Soundy and others 2014; Stubbs and others 2016). Future research should utilize objective measures of sedentary behavior. Accelerometers-inclinometers are available that allow for valid and reliable assessment of sedentary behavior. However, the association between sedentary behavior and cognitive functioning may be dependent on the domain/type of sedentary behavior (e.g., cognitively active sedentary behavior, such as reading and internet use, versus cognitively passive TV viewing), an aspect that is not reliably measured with accelerometers. Therefore, a combination of both objective and subjective methods is warranted. Finally, because this was a cross-sectional study, directionality is unclear, causality cannot be inferred and clearly future longitudinal or experimental research is required to better understand the current relationships. An important cohort to begin with to understand the relationship on sedentary behavior and cognitive decline, is older people with subjective memory deficits who do not have any objective memory loss, but are at increased risk of converting to MCI or dementia in the near future (Mitchell and others 2014), since this may be the critical time to potentially intervene on modifiable risk factors for objective cognitive deteriorations.

4.5. Conclusions

In conclusion, our study results suggest that a sedentary lifestyle might be a modifiable risk factor for MCI in LMICs. If confirmed in longitudinal and intervention studies, low-cost interventions

designed to minimize time spent sedentary might be a viable strategy to reduce the onset of cognitive decline and subsequent dementia in LMICs.

Acknowledgements

AK's work is supported by the Miguel Servet contract financed by the CP13/00150 and PI15/00862 projects, integrated into the National R + D + I and funded by the ISCIII - General Branch Evaluation and Promotion of Health Research - and the European Regional Development Fund (ERDF-FEDER).

BS is part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. BS is also supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. The views expressed are those of the author[s] and not necessarily those of the NHS, the NIHR or the Department of Health. JF is supported by a Blackmores Institute Fellowship.

Conflict of interest statement

The authors confirm that there are no financial conflicts of interest associated with this paper.

References

- Albert, M.S.; DeKosky, S.T.; Dickson, D.; Dubois, B.; Feldman, H.H.; Fox, N.C.; Gamst, A.; Holtzman, D.M.; Jagust, W.J.; Petersen, R.C. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*. 7:270-279; 2011
- Alzheimer's Disease International. World Alzheimer Report. 2014
- Alzheimer's Disease International. World Alzheimer Report. 2015
- Arokiasamy, P.; Uttamacharya; Kowal, P.; Capistrant, B.D.; Gildner, T.E.; Thiele, E.; Biritwum, R.B.; Yawson, A.E.; Mensah, G.; Maximova, T.; Wu, F.; Guo, Y.; Zheng, Y.; Kalula, S.Z.; Salinas Rodriguez, A.; Manrique Espinoza, B.; Liebert, M.A.; Eick, G.; Sterner, K.N.; Barrett, T.M.; Duedu, K.; Gonzales, E.; Ng, N.; Negin, J.; Jiang, Y.; Byles, J.; Madurai, S.L.; Minicuci, N.; Snodgrass, J.J.; Naidoo, N.; Chatterji, S. Chronic Noncommunicable Diseases in 6 Low- and Middle-Income Countries: Findings From Wave 1 of the World Health Organization's Study on Global Ageing and Adult Health (SAGE). *American journal of epidemiology*. 185:414-428; 2017
- Baumgart, M.; Snyder, H.M.; Carrillo, M.C.; Fazio, S.; Kim, H.; Johns, H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 11:718-726; 2015
- Biswas, A.; Oh, P.I.; Faulkner, G.E.; Bajaj, R.R.; Silver, M.A.; Mitchell, M.S.; Alter, D.A. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Annals of Internal Medicine*. 162:123-132; 2015
- Bull, F.C.; Maslin, T.S.; Armstrong, T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *Journal of physical Activity & Health*. 6: 790-804; 2009
- Christensen, K.; Doblhammer, G.; Rau, R.; Vaupel, J.W. Ageing populations: the challenges ahead. *Lancet*. 374:1196-1208; 2009
- Cummings, J.L. Treatment of Alzheimer's disease: current and future therapeutic approaches. *Reviews in neurological diseases*. 1:60-69; 2004
- Ekelund, U.; Steene-Johannessen, J.; Brown, W.J.; Fagerland, M.W.; Owen, N.; Powell, K.E.; Bauman, A.; Lee, I.-M.; Series, L.P.A.; Group, L.S.B.W. Does physical activity attenuate, or

- even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *The Lancet*. 388:1302-1310; 2016
- Falck, R.S.; Davis, J.C.; Liu-Ambrose, T. What is the association between sedentary behaviour and cognitive function? A systematic review. *Br J Sports Med*. 51:800-811; 2017a
- Falck, R.S.; Landry, G.J.; Best, J.R.; Davis, J.C.; Chiu, B.K.; Liu-Ambrose, T. Cross-sectional relationships of physical activity and sedentary behavior with cognitive function in older adults with probable mild cognitive impairment. *Physical Therapy*. 97:975-984; 2017b
- Ferri, C.P.; Jacob, K. Dementia in low-income and middle-income countries: Different realities mandate tailored solutions. *PLoS medicine*. 14:e1002271; 2017
- Ganesan, A.N.; Louise, J.; Horsfall, M.; Bilsborough, S.A.; Hendriks, J.; McGavigan, A.D.; Selvanayagam, J.B.; Chew, D.P. International mobile-health intervention on physical activity, sitting, and weight: the Stepathlon Cardiovascular Health Study. *Journal of the American College of Cardiology*. 67:2453-2463; 2016
- Gottesman, R.F.; Albert, M.S.; Alonso, A.; et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (aric) cohort. *JAMA Neurology*; 2017
- Johansson, L.; Guo, X.; Waern, M.; Ostling, S.; Gustafson, D.; Bengtsson, C.; Skoog, I. Midlife psychological stress and risk of dementia: a 35-year longitudinal population study. *Brain : a journal of neurology*. 133:2217-2224; 2010
- Kaduszkiewicz, H.; Zimmermann, T.; Beck-Bornholdt, H.P.; van den Bussche, H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *Bmj*. 331:321-327; 2005
- Katz, S.; Ford, A.B.; Moskowitz, R.W.; Jackson, B.A.; Jaffe, M.W. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *Jama*. 185:914-919; 1963
- Keadle, S.K.; Conroy, D.E.; Buman, M.P.; Dunstan, D.W.; Matthews, C.E. Targeting Reductions in Sitting Time to Increase Physical Activity and Improve Health. *Medicine and science in sports and exercise*; 2017

- Kessler, R.C.; Ustun, T.B. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res.* 13:93-121; 2004
- Kivipelto, M.; Ngandu, T.; Laatikainen, T.; Winblad, B.; Soininen, H.; Tuomilehto, J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.* 5:735-741; 2006
- Kowal, P.; Chatterji, S.; Naidoo, N.; Biritwum, R.; Fan, W.; Lopez Ridaura, R.; Maximova, T.; Arokiasamy, P.; Phaswana-Mafuya, N.; Williams, S.; Snodgrass, J.J.; Minicuci, N.; D'Este, C.; Peltzer, K.; Boerma, J.T. Data resource profile: the World Health Organization Study on global AGEing and adult health (SAGE). *International journal of epidemiology.* 41:1639-1649; 2012
- Ku, P.-W.; Liu, Y.-T.; Lo, M.-K.; Chen, L.-J.; Stubbs, B. higher levels of objectively measured sedentary behavior is associated with worse cognitive ability: Two-year follow-up study in community-dwelling older adults. *Experimental Gerontology.* 99:110-114; 2017
- Lara, E.; Koyanagi, A.; Domenech-Abella, J.; Miret, M.; Ayuso-Mateos, J.L.; Haro, J.M. The Impact of Depression on the Development of Mild Cognitive Impairment over 3 Years of Follow-Up: A Population-Based Study. *Dementia and geriatric cognitive disorders.* 43:155-169; 2017
- Lara, E.; Koyanagi, A.; Olaya, B.; Lobo, A.; Miret, M.; Tyrovolas, S.; Ayuso-Mateos, J.L.; Haro, J.M. Mild cognitive impairment in a Spanish representative sample: prevalence and associated factors. *International journal of geriatric psychiatry.* 31:858-867; 2016
- Lindbergh, C.A.; Dishman, R.K.; Miller, L.S. Functional Disability in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. *Neuropsychology review.* 26:129-159; 2016
- Livingston, G.; Sommerlad, A.; Orgeta, V.; Costafreda, S.G.; Huntley, J.; Ames, D.; Ballard, C.; Banerjee, S.; Burns, A.; Cohen-Mansfield, J. Dementia prevention, intervention, and care. *The Lancet*; 2017
- Mitchell, A.; Beaumont, H.; Ferguson, D.; Yadegarfar, M.; Stubbs, B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatrica Scandinavica.* 130:439-451; 2014
- Morris, J.C.; Heyman, A.; Mohs, R.C.; Hughes, J.P.; van Belle, G.; Fillenbaum, G.; Mellits, E.D.; Clark, C. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I.

- Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 39:1159-1165; 1989
- Moussavi, S.; Chatterji, S.; Verdes, E.; Tandon, A.; Patel, V.; Ustun, B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 370:851-858; 2007
- Pengpid, S.; Peltzer, K.; Kassean, H.K.; Tsala Tsala, J.P.; Sychareun, V.; Muller-Riemenschneider, F. Physical inactivity and associated factors among university students in 23 low-, middle- and high-income countries. *Int J Public Health*. 60:539-549; 2015
- Petersen, R.C. Mild Cognitive Impairment. *Continuum (Minneapolis, Minn)*. 22:404-418; 2016
- Powell, C.; Herring, M.; Dowd, K.; Donnelly, A.; Carson, B. The cross-sectional associations between objectively measured sedentary time and cardiometabolic health markers in adults—a systematic review with meta-analysis component. *Obesity Reviews*; 2017
- Prince, M.; Ali, G.-C.; Guerchet, M.; Prina, A.M.; Albanese, E.; Wu, Y.-T. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimer's research & therapy*. 8:23; 2016
- Prince, M.J. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends: Alzheimer's Disease International; 2015
- Prince, M.J.; Acosta, D.; Castro-Costa, E.; Jackson, J.; Shaji, K. Packages of care for dementia in low-and middle-income countries. *PLoS medicine*. 6:e1000176; 2009
- Rose, G.A. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ*. 27:645-658; 1962
- Sallis, J.F.; Bull, F.; Guthold, R.; Heath, G.W.; Inoue, S.; Kelly, P.; Oyeyemi, A.L.; Perez, L.G.; Richards, J.; Hallal, P.C. Progress in physical activity over the Olympic quadrennium. *Lancet*; 2016
- Sartori, A.C. The Relationship Between Inflammatory Biomarkers and Cognitive Function in Older Adults. University of Alabama at Birmingham, Graduate School; 2013
- Schuch, F.; Vancampfort, D.; Firth, J.; Rosenbaum, S.; Ward, P.; Reichert, T.; Bagatini, N.C.; Bgeginski, R.; Stubbs, B. Physical activity and sedentary behavior in people with major depressive disorder: A systematic review and meta-analysis. *Journal of Affective Disorders*. 210:139-150; 2017

- Schuch, F.B.; Vancampfort, D.; Sui, X.; Rosenbaum, S.; Firth, J.; Richards, J.; Ward, P.B.; Stubbs, B. Are lower levels of cardiorespiratory fitness associated with incident depression? A systematic review of prospective cohort studies. *Preventive Medicine*. 93:159-165; 2016
- Soundy, A.; Roskell, C.; Stubbs, B.; Vancampfort, D. Selection, use and psychometric properties of physical activity measures to assess individuals with severe mental illness: a narrative synthesis. *Archives of Psychiatric Nursing*. 28:135-151; 2014
- Stubbs, B.; Chen, L.-J.; Chang, C.-Y.; Sun, W.-J.; Ku, P.-W. Accelerometer-assessed light physical activity is protective of future cognitive ability: A longitudinal study among community dwelling older adults. *Experimental gerontology*. 91:104-109; 2017
- Stubbs, B.; Firth, J.; Berry, A.; Schuch, F.B.; Rosenbaum, S.; Gaughran, F.; Veronesse, N.; Williams, J.; Craig, T.; Yung, A.R.; Vancampfort, D. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression. *Schizophr Res*; 2016
- The Psychological Corporation. The Psychological Corporation: The WAIS III-WMS III Updated Technical Manual. San Antonio; 2002
- Tremblay, M.S.; Aubert, S.; Barnes, J.D.; Saunders, T.J.; Carson, V.; Latimer-Cheung, A.E.; Chastin, S.F.; Altenburg, T.M.; Chinapaw, M.J. Sedentary Behavior Research Network (SBRN)–Terminology Consensus Project process and outcome. *International Journal of Behavioral Nutrition and Physical Activity*. 14:75; 2017
- Vancampfort, D.; Stubbs, B.; Herring, M.; Hallgren, M.; Koyanagi, A. Sedentary behavior and anxiety: Association and influential factors among 42,469 community-dwelling adults in six low-and middle-income countries. *General Hospital Psychiatry*; 2017a
- Vancampfort, D.; Stubbs, B.; Koyanagi, A. Physical chronic conditions, multimorbidity and sedentary behavior amongst middle-aged and older adults in six low-and middle-income countries. *International Journal of Behavioral Nutrition and Physical Activity*. 14:147; 2017b
- Vancampfort, D.; Stubbs, B.; Lara, E.; Vandenbulcke, M.; Swinnen, N.; Koyanagi, A. Mild cognitive impairment and physical activity in the general population: Findings from six low- and middle-income countries. *Experimental Gerontology*. 100:100-105; 2017c
- World Health Organization. Global recommendations on physical activity for health: World Health Organization; 2010

- Wimo, A.; Guerchet, M.; Ali, G.C.; Wu, Y.T.; Prina, A.M.; Winblad, B.; Jonsson, L.; Liu, Z.; Prince, M. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 13:1-7; 2017
- Wirth, K.; Klenk, J.; Brefka, S.; Dallmeier, D.; Faehling, K.; i Figuls, M.R.; Tully, M.A.; Giné-Garriga, M.; Caserotti, P.; Salvà, A. Biomarkers associated with sedentary behaviour in older adults: a systematic review. *Ageing Research Reviews*. 35:87-111; 2017
- Zhai, L.; Zhang, Y.; Zhang, D. Sedentary behaviour and the risk of depression: a meta-analysis. *Br J Sports Med*. 49:705-709; 2015

Table 1

Sample characteristics

		Overall	Age 50-64 y	Age ≥65 y
Characteristic	Category	(N=32,715)	(N=19,092)	(N=13,623)
Sex	Female	51.7	50.1	54.5
Age (years)	Mean (SD)	62.1 (15.6)	56.3 (6.6)	72.3 (10.9)
Education (years)	Mean (SD)	6.1 (8.9)	6.5 (8.4)	5.3 (9.4)
Wealth	Poorest	16.9	14.4	21.3
	Poorer	18.9	17.7	21.0
	Middle	19.4	18.7	20.4
	Richer	21.5	23.8	17.5
	Richest	23.3	25.4	19.8
Depression	Yes	5.5	5.5	5.5
Obesity	Yes	11.5	12.2	10.4
No. of chronic physical conditions	Mean (SD)	1.3 (2.0)	1.2 (1.8)	1.6 (2.3)
Low physical activity	Yes	22.4	16.5	32.4
Mild cognitive impairment	Yes	15.3	13.5	18.5
Sedentary behavior	≥8h/day	10.1	7.7	14.4

Abbreviation: SD Standard deviation

Data are weighted column percentage unless otherwise stated.

Table 2

Association of highly sedentary behavior (≥ 8 h/day) and other covariates with mild cognitive impairment (outcome) estimated by multivariable logistic regression

Characteristic	Category	Overall (≥ 50 years)		50-64 years		≥ 65 years	
Sedentary behavior (h/day)	≥ 8 vs < 8	1.56***	[1.27,1.91]	1.34*	[1.02,1.76]	1.70***	[1.27,2.28]
Sex	Male vs. Female	0.96	[0.84,1.08]	0.82*	[0.71,0.96]	1.15	[0.96,1.39]
Age (years)	Per unit increase	1.02***	[1.01,1.03]	1.03**	[1.01,1.04]	1.05***	[1.04,1.06]
Education (years)	Per unit increase	0.97**	[0.95,0.99]	0.97**	[0.95,0.99]	0.98	[0.95,1.00]
Wealth	Poorest	1.00		1.00		1.00	
	Poorer	0.93	[0.78,1.11]	0.94	[0.76,1.16]	0.86	[0.65,1.12]
	Middle	1.00	[0.83,1.22]	0.88	[0.70,1.11]	1.11	[0.81,1.50]
	Richer	0.66***	[0.55,0.79]	0.65***	[0.51,0.83]	0.57***	[0.44,0.74]
	Richest	0.40***	[0.32,0.49]	0.33***	[0.25,0.43]	0.48***	[0.35,0.66]
Depression	Yes vs. No	0.93	[0.70,1.24]	0.91	[0.64,1.29]	0.90	[0.58,1.41]
Obesity	Yes vs. No	1.28*	[1.01,1.62]	1.47*	[1.09,1.98]	1.10	[0.77,1.56]
No. of chronic conditions	Per unit increase	1.14***	[1.08,1.21]	1.18***	[1.10,1.27]	1.12**	[1.04,1.22]
Low physical activity	Yes vs. No	1.19*	[1.03,1.39]	0.83*	[0.69,1.00]	1.58***	[1.26,1.99]

Data are odds ratio [95% confidence interval].

Models are mutually adjusted for all variables in the Table and country.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3

Association of increasing hours of sedentary behavior per day and other covariates with mild cognitive impairment (outcome) estimated by multivariable logistic regression

Characteristic	Category	Overall (≥50 years)	50-64 years	≥65 years
Sedentary behavior (h/day)	per one hour increase	1.08*** [1.05,1.11]	1.07*** [1.03,1.10]	1.09*** [1.05,1.13]
Sex	Male vs. Female	0.96 [0.85,1.09]	0.83* [0.71,0.97]	1.16 [0.96,1.39]
Age (years)	Per unit increase	1.02*** [1.01,1.02]	1.02** [1.01,1.04]	1.05*** [1.03,1.06]
Education (years)	Per unit increase	0.97*** [0.95,0.99]	0.97*** [0.95,0.99]	0.98 [0.95,1.00]
Wealth	Poorest	1.00	1.00	1.00
	Poorer	0.93 [0.78,1.11]	0.94 [0.76,1.17]	0.85 [0.65,1.12]
	Middle	1.00 [0.82,1.21]	0.87 [0.69,1.10]	1.10 [0.81,1.51]
	Richer	0.66*** [0.54,0.79]	0.65*** [0.51,0.83]	0.56*** [0.44,0.73]
	Richest	0.40*** [0.32,0.49]	0.32*** [0.25,0.42]	0.48*** [0.35,0.65]
Depression	Yes vs. No	0.92 [0.69,1.22]	0.90 [0.64,1.27]	0.89 [0.57,1.39]
Obesity	Yes vs. No	1.26 [1.00,1.59]	1.44* [1.08,1.94]	1.08 [0.76,1.55]
No. of chronic conditions	Per unit increase	1.14*** [1.08,1.21]	1.18*** [1.09,1.27]	1.12** [1.04,1.22]
Low physical activity	Yes vs. No	1.16* [1.00,1.35]	0.81* [0.67,0.97]	1.54*** [1.23,1.92]

Data are odds ratio [95% confidence interval].

Models are mutually adjusted for all variables in the Table and country.

* p<0.05, ** p<0.01, *** p<0.001

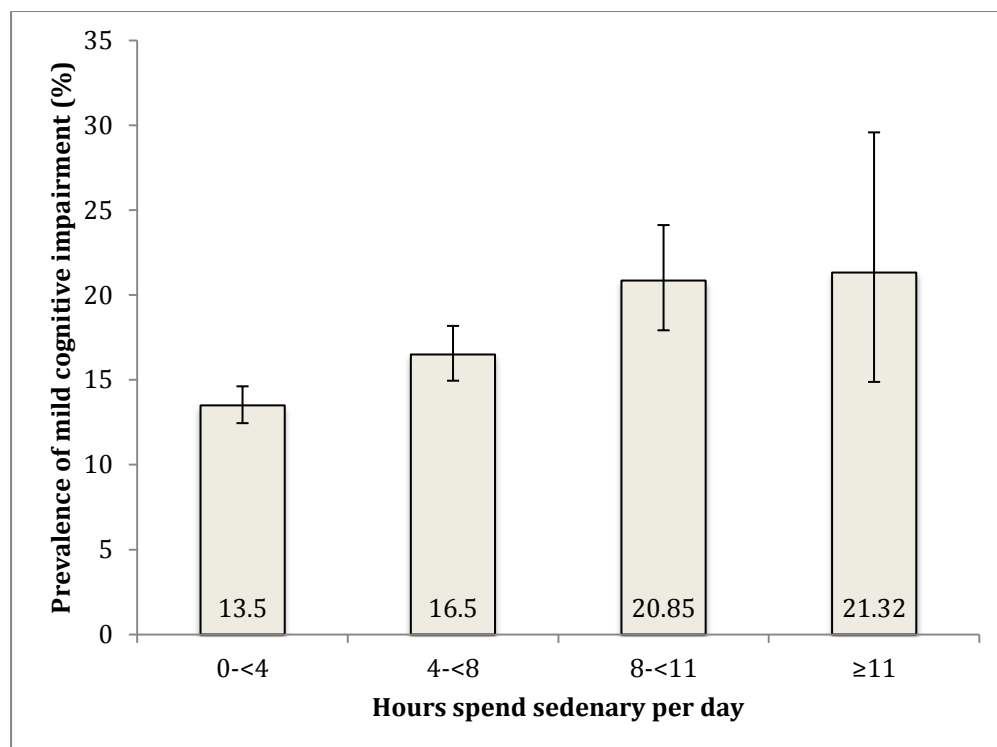


Figure 1

Prevalence of mild cognitive impairment by hours spent sedentary per day

Data are based on weighted sample.

Bars denote 95% confidence intervals.

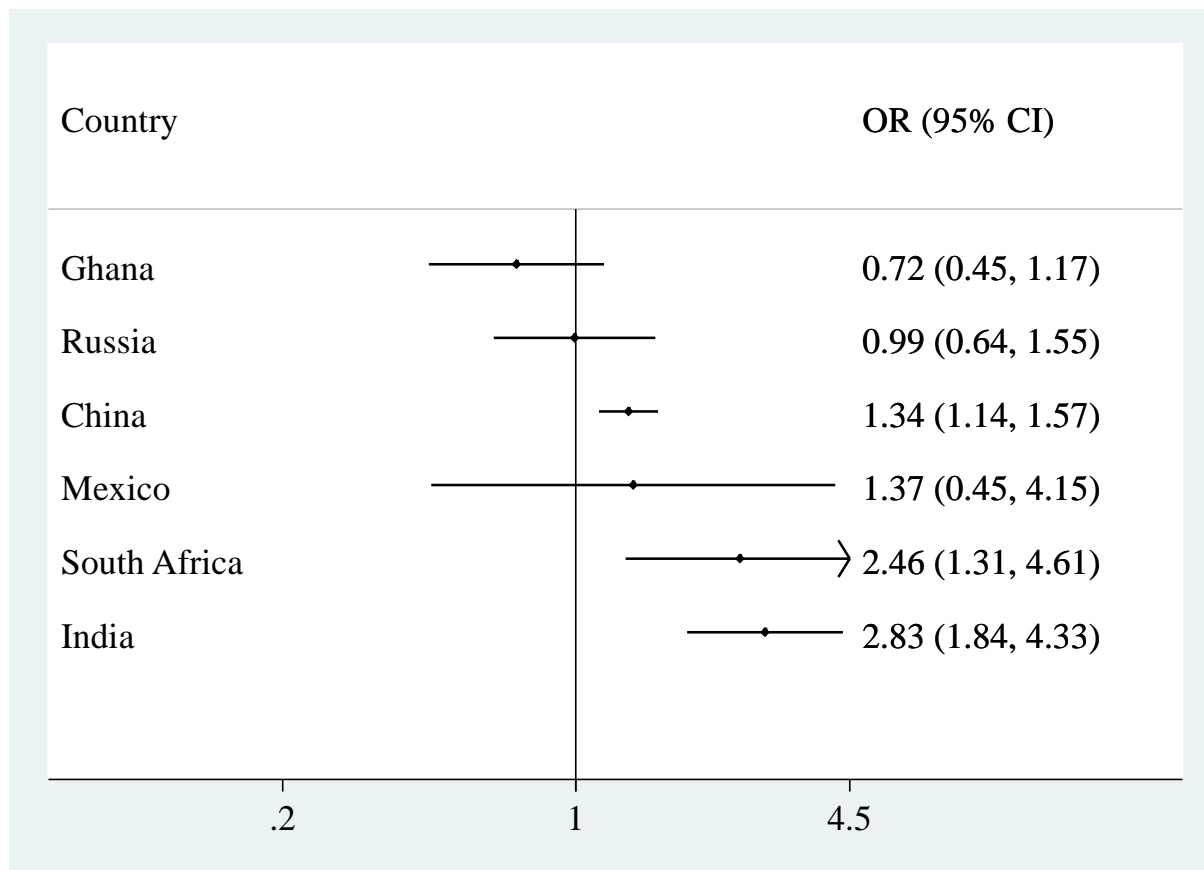


Figure 2

Country-wise association between highly sedentary behavior (exposure) and mild cognitive impairment (outcome) estimated by multivariable logistic regression

Abbreviation: OR Odds ratio; CI Confidence interval

Highly sedentary behavior referred to being sedentary for ≥ 8 hours/day.

Models are adjusted for age, sex, education, wealth, depression, obesity, number of chronic physical conditions, and low physical activity.

Highlights

- Being sedentary might be a risk factor for mild cognitive impairment.
- Every hour spent sedentary is associated with a higher mild cognitive impairment risk.
- Physical, mental health and social factors likely affect the relationship.